Original Article

The association of carbohydrate intake, glycemic load, glycemic index, and selected rice foods with breast cancer risk: a case-control study in South Korea

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Despite carbohydrate hypothesis related to breast cancer development, the inter-relationships of carbohydrate measures with risk of breast cancer are unclear. We evaluated the association between the risk of breast cancer and total carbohydrate intake, glycemic load, and glycemic index, and types of rice in a hospital-based case-control study. Cases were 362 women aged 30-65 years old who were histologically confirmed to have breast cancer. Controls visiting the same hospital were matched to cases according to their age (±2 years) and menopausal status. Food intake was estimated by a quantitative food frequency questionnaire (FFQ) with 121 items. Conditional and unconditional logistic regression analysis was used to obtain the odds ratios (ORs) and corresponding 95% confidence intervals. There were no associations between risk of breast cancer and carbohydrate intake and glycemic load. A positive association with white rice (OR=1.19 per 100 g/d increment, 95% confidence interval (CI)=1.01-1.40), no association with mixed white rice (OR=0.95 per 100 g/d increment, 95% CI=0.80-1.13), and an inverse association with mixed brown rice (OR=0.76 per 100 g/d increment of mixed brown rice, 95% CI=0.61-0.95) was found. Additional analysis showed a positive association for white rice and an inverse association for mixed brown rice with breast cancer risk among overweight, postmenopausal women. These results do not support an association between breast cancer and diets high in carbohydrate, glycemic index, or glycemic load. However, a higher consumption of mixed brown rice may be associated with a decreased risk of breast cancer, especially in overweight, postmenopausal women.

Key Words: carbohydrate, glycemic load, glycemic index, rice, breast cancer

INTRODUCTION

Some researchers have hypothesized that carbohydrates may promote cancer growth by increasing insulin levels or insulin-like growth factor I (IGF-I) levels.[1-2] The physiological mechanisms which may underlie the increase in circulating total IGF-I and insulin have been investigated. Among them, chronic energy restriction may cause a dramatic drop in circulating IGF-I levels, but obesity and physical activity was not related with IGF-I and reduced insulin levels appeared with physical activity, weight loss, and a high fiber diet.[1-2] It is unclear how elevated IGF-I or insulin levels may be related to diet. Nevertheless, rapidly-digestible and absorbable carbohydrates may contribute to elevated IGF-I or insulin levels.[1,3] A measure of the relative impact of carbohydrate-containing foods on blood glucose is the glycemic index (GI), developed by Jenkins and colleagues in 1981.[4] Rapidly-digestible and absorbable carbohydrates have a high GI. The product of the GI value of a food and its carbohydrate content was also defined by the concept of glycemic load (GL). These measures allow simultaneous assessment of both the quality and quantity of the carbohydrate consumed.[5] A review on diet and breast cancer showed that the most recent studies on carbohydrates and breast cancer risk have included the GL and the GI as carbohydrate nutrition factors.[6] However, most previous studies using GI and GL have not revealed an association with breast cancer risk.[6]

Carbohydrate sources range from simple sugars such as mono- and disaccharides to starches. GL and GI have been used as indicators of the quality and quantity of carbohydrates with respect to blood glucose and insulin response after carbohydrate consumption. However, given the chemical and physical complexity of food, as well as the variety of defense mechanisms against carcinogenesis, it is difficult to assign an anticarcinogenic or a carcinogenic effect to an isolated component of consumed food.

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Cooked rice is the most frequently consumed staple food item for Koreans and provides more than 55% of daily carbohydrate intake. On average, 97% of men and 95% of women eat more than twice daily.[7] Although all Koreans eat rice, there are several types of cooked rice, including refined white rice, white rice with cereals and/or beans (mixed white rice), and brown rice with cereals and/or beans (mixed brown rice). Components in whole grains associated with improved health status include dietary fiber, vitamins, minerals, lignans, phytoestrogens, phenolic compounds, and phytic acid, and these components coexist with starch highly concentrated in endosperm.[8] Therefore, it may be difficult to dissociate the effect of carbohydrates on breast cancer from other components in the same carbohydrate source. However, the refining process removes most of bran and some of the germ, thus the relative concentration of starch is higher in refined grains.[8]

In the present study, the association of breast cancer risk with the dietary intake of carbohydrates, GL, and GI among Korean women was examined. Additionally, it was evaluated whether the source foods of carbohydrate such as white rice and brown rice differently affects breast cancer risk.

MATERIALS AND METHODS

Recruitment of cases and controls

Cases and controls were recruited from October 2004 through June 2006 at Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea. All participants aged 30-65 years were examined by mammography to detect any possibility of breast cancer. Cases had histologically confirmed breast cancer and controls were patients visiting one of the dentistry, orthopedic surgery, general surgery, ophthalmology, dermatology, rehabilitation, or family medicine clinics within the same hospital. We excluded participants who had any history of cancer (5 cases) or had estimated total energy intakes <500 kcal/d or >4000 kcal/d (16 cases and 13 controls). Cases and controls were matched with respect to age (±2 years) and menopausal status (362 pairs). This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Institutional Review Board of the Samsung Hospital at Sungkyunkwan University. Written informed consent was obtained from each participant.

Data Collection

Cases and controls were interviewed by trained interviewers with a questionnaire that consisted of general characteristics, menstrual and reproductive history, familial history of breast cancer, smoking, drinking, intake of multivitamins, and the average time spent exercising. Dietary data was collected by the quantitative food frequency questionnaire (FFQ), modified from a validated FFQ,[9] with visual aids such as food photographs and models for item specific units. The validity and reliability for the total carbohydrates was acceptable (correlation coefficient with multiple 24 hour recalls=0.47; correlation coefficient between two FFQs=0.41), although it was not formally validated for GI and GL. The FFQ was composed of 121 food items which included some rice foods such as white rice, mixed white rice, and mixed brown rice. Open-ended questions with standard units such as cup, bowl, and piece etc were used. Subjects were asked by trained interviewers to recall their usual intake of the 121 food items over a period of 12 months beginning from 3 years prior to the time of the interview.[10] The average frequency of foods consumed was asked in nine categories ranging from never or less than once per month to three times or more per day. All frequencies were standardized into "times per day" by using the conversion factors 30.4 days or 4.3 weeks per month. Daily food and nutrient intake was calculated with a standardized frequency per day and amount of food consumed. Detailed information on database collection has been presented in previous publications elsewhere.[11-12]

Three carbohydrate measures were used: carbohydrate intake, GL and GI. To determine GL consumption, the carbohydrate content of each food item was multiplied by its GI value, and then all of the GL values were summed. The overall dietary GI was calculated by dividing the average daily GL by the average daily carbohydrate intake. The GI value for each food item was obtained from the international table of GI values,[13] the GI online database maintained by the University of Sydney.[14] The reference GI value was glucose (GI for glucose=100). When several GI values were available for a food item, the mean GI value was used. For foods for which a GI value had not been determined, a value was assigned based on the most similar food item. In the case of mixed dishes, the GI value for each ingredient was directly assigned with the GI value of GI databases from the recipe, such as boiled or raw. To get the GL value for each ingredient, the matched GI value was multiplied by the carbohydrate content of that ingredient. The GL value for mixed dishes was obtained by summing the GL values of all of the ingredients. The overall GI value of each mixed dish was also calculated by dividing the GL value by the carbohydrate content of that mixed dish. Therefore, the mean value of twelve studies on GI for white rice and that of three studies for brown rice was assigned (64 and 55, respectively) and overall GI values calculated from each ingredient were assigned for mixed white rice and mixed brown rice (62 and 54, respectively) (Table 1). Food items with a zero or negligible carbohydrate content, such as meat, fish, poultry, eggs, fats, and oils, were assumed to produce little glycemic response and were not assigned GI values. Of the 121 food items listed in the FFQ, GI values were calculated for 79 items with GI values ranging from 14 (peanuts) to 105 (starch syrup). In the present study, the carbohydrate content of these 79 food items contributed to 96.5% (SD=2.2) of the total available carbohydrate intake.

To examine whether the effect of the sources of carbohydrates on breast cancer risk was different, the association between different rice foods, which are major contributors to the daily intake of carbohydrates (16% for mixed brown rice; 19% for mixed white rice; 33% for white rice) or GL (16% for mixed brown rice; 20% for mixed white rice; 21% for white rice) and breast cancer was analyzed (Table 1).

Table 1. The contribution of some rice foods to carbohydrate and glycemic load

		Carbohydrate for controls			Glycemic load for controls		
	Glycemic index (glucose=100)	Mean±SD	% carbohydrate from each food	Percentage of contribution to variation (%)[1]	Mean±SD	% glycemic load from each food	Percentage of contribution to variation (%)[1]
White rice, g/d	64	63 ± 91	20	33	40 ± 58	21	10
Mixed white rice	62	62 ± 91	19	10	38 ± 57	20	34
Mixed brown rice	54	58 ± 102	16	12	31 ± 55	16	5

Only food items contributing to more than 5% of total energy-unadjusted carbohydrate and glycemic load were shown. Carbohydrate, GI, and GL were adjusted for total energy intake (kcal/d) by residual method.

† Partial R^2 from multiple stepwise regression with carbohydrate intake or glycemic load as the dependent variable and carbohydrate intake or glycemic load from each food as the independent variable.

Statistical analysis

All nutrient intakes were total energy-adjusted values by the residual method.[15] Cases and their matched controls were compared by a paired *t*-test for continuous variables and by the McNemar test for categorical variables. The quintiles of dietary carbohydrate, GI, GL, and other nutrient intakes and the quantiles of daily rice food intake were used in the analyses. The general linear model and the Cochran-Mantel-Haenszel analysis were used to assess potential confounders among controls. Variables which were significantly different between cases and controls and showed significant linear trends across quintiles of carbohydrate, GI, and GL were adjusted in the multivariable models. Conditional logistic regression analysis was applied to obtain the odds ratios (ORs) and corresponding 95% confidence intervals (CI). The trend tests were conducted by considering the median values of each quantile of dietary carbohydrate, GI, GL, and rice intakes as continuous values in each of the model. Daily carbohydrate, GI, GL, and rice food intakes were introduced as continuous values, and the units were expressed in increments of 100 g/d, 50 units/d, 10 units/d, and 100 g/d, respectively. After stratification by weight status (BMI <23 or ≥23 kg/m^2),[16] an unconditional logistic regression was used for the multivariable analysis. All statistical analyses were conducted using SAS software (version 9.2, SAS Institute Inc., Cary, NC).

RESULTS

The comparisons of some general characteristics and the average of dietary nutrient and foods intakes between cases and controls are presented in Table 2. The average age of the cases and controls was 46 years, and the proportion of menopausal women was 35%. Women in the control group had more children and higher proportions of multivitamin use and breastfeeding than those in the case group. Although the proportion of alcohol drinkers was higher in the controls than in the cases, the daily consumption of alcohol (g/d) was not significantly different between the cases and controls. The number of drinkers was very low, and the proportion of drinkers who had one or more drinks was approximately 3% in both case and control patients in the present study. The average carbohydrate and white rice intake and glycemic index was higher in cases than in controls. However, mixed white rice and brown rice was higher in controls, although not statistically significant.

Table 3 presents selected characteristics of study participants according to quintiles of carbohydrate intake, GL, and overall GI among controls. Higher carbohydrate intake was related to higher postmenopausal status, older age, white rice intake, mixed white rice consumption, mixed brown rice intake, a lower proportion of multivitamin use, and daily intake of folate, soy protein, and vitamin E. A higher dietary GL was related to older age, a higher daily intake of carbohydrates, white rice, mixed white rice and a lower daily intake of soy protein, fiber, folate, vitamin E, and mixed brown rice. In the case of GI, higher intake was related with a higher BMI, a higher intake of carbohydrates, and mixed white rice, and a lower daily intake of soy protein, fiber, folate, vitamin E, and mixed brown rice. The GI of the diet was uncorrelated with carbohydrate. Total fat intake was not included in the analyses because of the strong correlation with total carbohydrate intake (r= –0.70), and there was no difference between cases and controls.

The association between the intake of carbohydrate, GL, GI, and rice food type and breast cancer risk is shown in Table 4. A higher carbohydrate intake was positively associated with breast cancer risk in the crude model (5th vs. 1st quintile; OR=1.92, 95% CI=1.19-3.11, *p* for trend=0.01), and a 61% increased risk per 100 g/d increment of carbohydrate intake was also found. However, the adjustment for potential confounders, including dietary factors such as soy protein, folate, vitamin E, and fiber, attenuated the strength of the association (multivariable model). No association between GL and breast cancer risk was found in the present study. An inverse association between GI and breast cancer risk was found in the crude model for the continuous value (34% decreased risk per 10 units/d increment) and in the multivariable model (5th vs. 1st quintile; OR=0.44, 95% CI= 0.23-0.85, *p* for trend=0.01, 42% decreased risk per 10 units/d increment in multivariable model).

Interestingly, rice, which is major contributor of daily intake in this study population, was differently associated with breast cancer risk. A higher intake of white rice was associated with an increased breast cancer risk (the highest vs. 1st quantile; OR=1.48, 95% CI=1.02-2.16, *p* for trend=0.01 in the crude model) and a 100-g/d increment increased the risk by 20%. Although the adjustment for potential confounders attenuated the statistical significance of the association between white rice and breast cancer, the increased risk per 100 g/d increment of white rice remained (OR=1.19 per 100 g/d, 95% CI=1.01-1.40).

Table 2. General characteristics and estimated nutrient and food intakes related to carbohydrate exposures among Korean women based on a matched case-control study (362 pairs)

Characteristics	Cases (n=362)	Controls (n=362)	*p*-value
Age, y	46.1± 8.5	46.0 ± 8.6	N/A
Menopause,%	35	35	N/A
Education, y	12.7 ± 3.6	12.4 ± 3.5	0.31
Body mass index, Kg/m^2	23.6 ± 3.2	23.4 ± 3.0	0.41
Family history of breast cancer, %	8	12	0.10
Current smokers, %	1.9	3.9	0.13
Current alcohol drinkers, %	29	38	<0.01
Alcohol consumption, g/d	1.85 ± 6.14	2.40 ± 8.07	0.29
Regular exercise (MET-hours/wk ≥ 22.5), %	17	22	0.11
Multivitamin users, %	8.8	14	0.03
Reproductive factors			
Nulliparous, %	11	8	0.13
Number of children, N	1.9 ± 1.0	2.1 ± 1.0	0.01
Breast feeding, %	64	77	<0.0001
Oral contraceptive use, %	15	14	0.83
Used hormone compound, %	14	14	0.82
Age at menarche, y	14.5 ± 1.7	14.5 ± 1.7	0.41
Age at the first birth, y	26 ± 3.5	26 ± 3.4	0.84
Age at menopause, y	48 ± 5.4	48 ± 5.1	0.11
Nutrient and food intakes			
Total energy, kcal/d	1945 ± 572	2026 ± 658	0.07
Carbohydrate, g/d	320 ± 41	312 ± 41	0.008
Fat, g/d	40.9 ± 13.0	42.6 ± 13.3	0.07
Glycemic load	181 ± 33	182 ± 32	0.53
Glycemic index	58 ± 7.5	57 ± 5.5	0.02
Soy protein, g/d	7.4 ± 4.5	8.5 ± 4.6	0.001
Folate, µg/d	284 ± 100	297 ± 100	0.07
Vitamin E, mg/d	10.6 ± 4.1	11.2 ± 4.3	0.09
Fiber, g/d	10.1 ± 4.5	10.1 ± 4.1	0.96
Total vegetables, g/d	84 ± 165	83 ± 89	0.99
Total fruits, g/d	312 ± 385	278 ± 246	0.16
The main staple foods in Korea			
White rice, g/d	110±137	82±119	0.003
Mixed white rice	65±117	82±122	0.07
Mixed brown rice	70±124	79±139	0.36

N/A, not applicable
Values are expressed as Mean ± SD or Percent
All nutrient intakes were adjusted for total energy intake (kcal/d) by the residual method
p-value: paired *t* test for continuous variables or McNemar test for categorical variable.

In contrast, mixed brown rice were inversely associated with breast cancer risk in multivariable models (for mixed brown rice with cereals and beans: the highest vs. 1st quintile; OR=0.42, 95% CI=0.20-0.87, *p* for trend=0.01, 24% decreased risk per 100 g/d).

Many large epidemiological studies have found that overweight or obese postmenopausal women are at increased risk of developing breast cancer.[17] Insulin levels are higher in the presence of insulin resistance and obesity.[18,19] Therefore, we evaluated whether the associations by weight status were dependent on menopausal status with continuous dietary data after stratifying subjects into four groups (Table 5): 1) premenopausal women with normal weight status; 2) premenopausal women with overweight status; 3) postmenopausal women with normal weight status; and 4) postmenopausal women with overweight status. The GI was inversely associated with breast cancer among overweight women both with premenopausal status (OR=0.38, 95% CI=0.17-0.86) and postmenopausal status (OR=0.48, 95% CI=0.23-0.99). An increased risk for breast cancer per 100g/d increment of white rice in postmenopausal women with overweight status (OR=1.47, 95% CI=1.04-2.07) was found. Decreased risk per 100 g/d increment

Table 3. Selected characteristics according to the quintiles of estimated dietary carbohydrate intake, glycemic load, and glycemic index among controls based on a matched case-control study (362 pairs)

	Quintiles of carbohydrate intake				Quintiles of glycemic load				Quintiles of glycemic index			
	Q1	Q3	Q5	*p* for trend	Q1	Q3	Q5	*p* for trend	Q1	Q3	Q5	*p* for trend
Median	261	316	369		143	180	222		51	57	63	
Age (yr)	44	46	51	<.0001	44	46	48	0.008	48	44	46	0.24
Menopause (yes)	29	33	41	0.05	32	35	40	0.07	51	57	63	0.37
Education (year)	12.2	12.7	11.5	0.27	12.2	12.0	11.7	0.07	12.8	12.2	12.5	0.22
Body mass index (kg/m^2)	23.3	23.5	23.4	0.75	23.2	23.6	23.7	0.22	23.1	23.0	24.0	0.03
Family history of breast cancer (%)	8	9	24	0.11	10.0	14.8	14.8	0.39	10.4	5.5	12.4	0.38
Current smoker (%)	3.2	7.2	0	0.66	3.8	6.4	1.8	0.59	4.6	7.8	2.7	0.59
Current alcohol drinker (%)	43	37	35	0.40	48	31	35	0.31	37	34	35	0.60
Physical activity (≥22.5MET-hours/wk, %)	28	18	17	0.13	26	20	17	0.34	27	28	21	0.28
Multivitamin user (%)	22	14	9	0.02	17	13	13	0.26	15	17	17	0.91
Parity (%)	89	92	96	0.22	88	91	92	0.31	86	95	90	0.49
Number of children	2.1	2.1	2.1	0.89	2.1	2.1	2.1	0.54	2.0	2.3	2.0	0.96
Oral contraceptive use (ever, %)	17	17	11	0.36	22	15	16	0.64	13	14	16	0.46
Breastfeeding (ever, %)	76	78	83	0.42	71	76	80	0.24	73	78	74	0.49
Dietary intake of												
Total Energy (kcal/d)	1963	2071	1936	0.81	2.17	2047	1937	0.75	2052	2004	1991	0.33
Soy protein (g/d)	9.2	8.8	6.8	0.002	9.5	8.2	6.7	<.0001	10.9	8.6	7.1	<.0001
Fiber (g/d)	9.3	10.7	10.0	0.10	10.7	10.6	7.7	<.0001	14.7	9.1	7.9	<.0001
Folate (μg/d)	301	309	247	0.009	317	304	244	<.0001	361	291	263	<.0001
Vitamin E (mg/d)	12.5	12.0	8.1	<.0001	13.3	11.6	8.1	<.0001	14.4	10.4	10.0	<.0001
Carbohydrate (g/d)	256	317	368	<.0001	261	317	351	<.0001	296	306	314	0.006
Glycemic load	150	179	220	<.0001	143	180	222	<.0001	148	174	210	<.0001
Glycemic index	58	57	60	0.71	53	57	66	<.0001	50	57	67	<.0001
White rice (g/d)	67	79	105	0.02	46	66	138	<.0001	12	75	128	0.15
Mixed white rice with cereals and beans (g/d)	45	72	136	<.0001	43	88	133	<.0001	27	120	74	0.01
Mixed brown rice with cereals and beans (g/d)	45	95	105	0.006	77	98	19	0.008	191	40	20	<.0001

The prevalence of menopausal status and age were adjusted for respectively and other variables were adjusted for both age and menopausal status. Values were expressed as a mean or percent. *P*-values for the trends were determined by the general linear model for continuous variables and by the Cochran-Mantel-Haenszel test for categorical variables.

Table 4. Odds ratio (OR) and 95% confidence intervals (CIs) for breast cancer risk according to carbohydrate intake, glycemic load, glycemic index, and rice foods among Korean women based on a matched case-control study (362 pairs)

	Quintiles of carbohydrate intake, glycemic load, and glycemic index/ Quantiles of rice foods					*p* for trend	Continuous
	Q1	Q2	Q3	Q4	Q5		
Carbohydrate intake							
Median	261	294	316	342	369		per 100g/d
Cases/Controls	61 / 83	73 / 72	68 / 77	76 / 69	84 / 61		
Crude OR	1.0	1.38 (0.86, 2.21)	1.17 (0.74, 1.86)	1.48 (0.93, 2.35)	1.92 (1.19, 3.11)	0.01	1.61 (1.13, 2.30)
Multivariable OR†	1.0	1.38 (0.82, 2.33)	1.04 (0.61, 1.79)	1.14 (0.66, 1.99)	1.59 (0.88, 2.87)	0.28	1.38 (0.88, 2.16)
Glycemic load							
Median	143	164	180	197	222		per 50 units/d
Cases/Controls	73 / 71	67 /78	64/ 81	79 / 66	79 / 66		
Crude OR	1.0	0.80 (0.50, 1.29)	0.76 (0.47, 1.21)	1.12 (0.71, 1.75)	1.15 (0.73, 1.81)	0.24	1.07 (0.86, 1.34)
Multivariable OR	1.0	0.89 (0.52, 1.53)	0.62 (0.36, 1.07)	0.99 (0.57, 1.69)	0.85 (0.48, 1.50)	0.80	0.91 (0.69, 1.20)
Glycemic index							
Median	51	54	57	59	63		per 10 units/d
Cases/Controls	79 / 65	69 / 76	74 / 71	74 / 71	66 / 79		
Crude OR	1.0	0.75 (0.47, 1.20)	0.88 (0.55, 1.41)	0.87 (0.55, 1.37)	0.70 (0.44, 1.10)	0.22	0.76 (0.60, 0.97)
Multivariable OR	1.0	0.75 (0.44, 1.27)	0.79 (0.42, 1.47)	0.62 (0.32, 1.21)	0.44 (0.23, 0.85)	0.01	0.58 (0.41, 0.82)
White rice							
Median	0	39	180	315			per 100 g/d
Cases/Controls	178/189	23/44	74/70	87/59			
Crude OR	1.0	0.57 (0.33, 1.99)	1.10 (0.75, 1.63)	1.48 (1.02, 2.16)		0.01	1.18 (1.06, 1.33)
Multivariable OR	1.0	0.77 (0.41, 1.45)	1.10 (0.67, 1.81)	1.51 (0.90, 2.54)		0.10	1.19 (1.01, 1.40)
Mixed white rice with cereals and beans							
Median	0	79	350				per 100 g/d
Cases/Controls	241/197	54/88	67/77				
Crude OR	1.0	0.51 (0.34, 0.75)	0.74 (0.50, 1.08)			0.09	0.90 (0.79, 1.01)
Multivariable OR	1.0	0.67 (0.42, 1.08)	0.97 (0.57, 1.66)			0.90	0.95 (0.80, 1.13)
Mixed brown rice with cereals and beans							
Median	0	100	350				per 100 g/d
Cases/Controls	252/244	44/43	66/75				
Crude OR	1.0	0.98 (0.62, 1.57)	0.85 (0.59, 1.24)			0.41	0.95 (0.85, 1.06)
Multivariable OR	1.0	0.90 (0.47, 1.71)	0.42 (0.20, 0.87)			0.01	0.76 (0.61, 0.95)

OR, Odds Ratio; CI, 95% confidence interval
†Multivariable included BMI (kg/m^2, continuous), alcohol drinking (none, past, current), multivitamin use (yes, no), number of children, breast feeding (yes, no), and dietary factors including soy protein (quintiles), folate (quintiles), vitamin E (quintiles), and fiber (quintiles).

Table 5. Odds ratio (OR) and 95% confidence intervals (CIs) for breast cancer risk according to carbohydrate intake, glycemic load, glycemic index, and rice foods by menopausal and weight status among Korean women based on a matched case-control study (362 pairs)

	Premenopausal status		Postmenopausal status	
	Normal Weight (BMI <23)	Overweight status (BMI ≥23)	Normal Weight (BMI <23)	Overweight status (BMI ≥23)
No of cases/controls	123/144	112/91	36/41	91/86
Carbohydrate intake, per 100g/d	1.38 (0.59, 2.88)	0.93 (0.38, 2.26)	0.01 (0.001, 11.0)	2.54 (0.87, 7.41)
Glycemic load, per 50 units/d	0.89(0.57, 1.39)	0.64 (0.34, 1.20)	0.22 (0.01,6.22)	1.02 (0.54, 1.95)
Glycemic index, per 10 units/d	0.66 (0.39, 1.10)	0.38 (0.17, 0.86)	1.25 (0.19, 8.31)	0.48 (0.23, 1.00)
White rice, per 100 g/d	1.06 (0.80, 1.41)	1.14 (0.83, 1.57)	0.35 (0.06, 2.10)	1.47 (1.04, 2.07)
Mixed white rice with cereals and beans, per 100 g/d	0.90 (0.67, 1.21)	0.90 (0.62, 1.91)	0.82 (0.21, 3.12)	1.05 (0.74, 1.50)
Mixed brown rice with cereals and beans, per 100 g/d	0.88 (0.58, 1.34)	0.80 (0.52, 1.21)	0.25 (0.03, 1.82)	0.58 (0.37, 0.90)

Odds ratios were obtained by unconditional logistic regression analysis after adjusting for age, alcohol drinking (none, past, current), multi-vitamin use (yes, no), number of children, breast feeding (yes, no), and dietary factors such as soy protein (quintiles), folate (quintiles), vitamin E (quintiles), and fiber (quintiles) as covariates

of mixed brown rice was found only in postmenopausal women with overweight status (OR=0.58, 95% CI=0.37-0.90).

DISCUSSION

There was no increased risk of breast cancer with high dietary intake of carbohydrate and GL, and high-GI. A higher intake of white rice was related to an increased risk for breast cancer among overweight, postmenopausal women, whereas a higher intake of mixed brown rice was related to a decreased risk for breast cancer among overweight, postmenopausal women.

In vitro or animal studies have shown that insulin or IGF-I may directly affect tumor development by stimulating cell proliferation, by inhibiting apoptosis, and by modifying endogenous sex steroid metabolism.[1] Theoretically, rapidly-digestible and absorbable carbohydrates, foods with a high GI, may elevate IGF-I or insulin levels and may be associated with breast cancer risk. However, in the present study, any increased risk was not found with high carbohydrate, GL, or GI. Unlike the GI and breast cancer hypothesis, an inverse association between GI and breast cancer risk was found in the present study. Previously, there were a few case-control studies and some prospective studies investigating the links between dietary carbohydrates, GL, or GI and breast cancer, but most of those studies have not supported the hypothesis of GI and breast cancer risk.[20-36] Among prospective cohort studies on carbohydrate intake, eleven out of twelve studies showed null associations with breast cancer.[23-30,32-33,35-36] One small follow-up study showed an elevated risk of breast cancer with increased carbohydrate.[30] A nested case-control study showed a decreased incidence of breast cancer with increased carbohydrate intake (RR=0.42 across tertiles, 95% CI=0.18-0.95) among postmenopausal women.[37] Nine cohort studies have looked at GL and GI,[25-28,31,32,34-36] but only the Nurses' Health Study and the Canadian National Breast Screening Study showed an increased risk of breast cancer with GL and GI among postmenopausal women, respectively.[27,28] A French cohort study showed an increased risk with GL and GI among overweight postmenopausal women.[36] Among premenopausal women, only the Hormones and Diet in the Etiology of Breast Tumors Study (ORDET Study), out of five cohort studies, showed an increased risk of breast cancer with GI and GL.[26-28,34,35] It is unclear why high GI was rather inversely associated with breast cancer risk in the present study unlike previous studies. A possible explanation is that GI may be a simple marker of another health-related behavior in Korea. However, in the present study, a high GI was related to unhealthy characteristics, relatively high BMI and a high intake of carbohydrate and low intake of soy protein, fiber, folate, vitamin E, and mixed brown rice. Another concern is the usefulness of GI. Although the glycemic index is a significant predictor of the insulin response, only 23% of the variability in insulinemia is accounted for by the glycemic index.[38] The glycemic response may not be an adequate marker of insulin or IGF-I response and an insulin index of food may be a better measure of the potential hyperinsulinemic effect of food.

There have not been many prior studies that have examined the association between rice type and breast cancer risk, except for an ecological study that reported that populations with lower rates of breast cancer are more likely to have higher consumption of rice;[39] however, no study has shown a link between refined grain intake and breast cancer risk.[40] The present study findings show significant but different results based on the type of rice. A significantly positive association between white rice and breast cancer among overweight women was found in postmenopausal women (OR=1.47, 95% CI=1.04-2.07 in Table 4). However, there was no association between mixed white rice and breast cancer risk. Mixed brown rice was inversely associated with breast cancer only among overweight postmenopausal women (OR=0.58 per 100 g/d increment of mixed brown rice, 95% CI=0.37-0.90). It is interesting that there were different associations between different rice foods and breast cancer risk. The positive association with white rice may indicate that eating only the starchy endosperm of rice, which is composed primarily of starch and therefore has a high GI, may increase breast cancer risk. It might indirectly support the hypothesis of breast cancer risk linked to carbohydrate in obese women by Holmes *et al.*[27] The lack of an association between mixed white rice and breast cancer risk may be due to the anticarcinogenic components of mixed cereals and beans.[8] The inverse association between brown rice intake and breast cancer risk is biologically reasonable because of the high nutritional quality of brown rice; the great bulk of nutrients and biologically active constituents in grain are found in the bran and the germ.[8]

Taken together, these findings suggest that a weak association or an unexpected association of carbohydrate measures with breast cancer may be attributed to the characteristics of the carbohydrate source ingested.

Several limitations should be considered when interpreting the findings of this study. The primary concern is that the present study was a hospital-based case-control study, thus, there is a restriction in generalizing the results to the general population.[41] Another potential bias in a case-control study is that cases could change their diet as a result of cancer diagnosis and treatment. However, in the present study, all cases were interviewed before diagnosis or within one week after diagnosis so that dietary changes of cases or differential recall biases are not substantial. In addition, the selection of an appropriate control group may be problematic.[41] The diets of those who participated the study may still differ from those who did not participate. Another limitation in interpreting results is that the FFQ was not specifically designed to investigate the association between GI or GL or rice with breast cancer risk and it was not formally validated for them. Furthermore, the values were generated from international tables and did not reflect the mixed foods eaten at the same time which does influence GL. However, we observed strong relationships between GI and GL and low HDL cholesterolemia among women (OR=1.77 per increment 10 units of GI, 95% CI=1.06-2.93; OR=2.21 per 50 units/d increment of GL, 95% CI=1.47-3.33 in a general population in a rural area) with the same GI database in another study,[42] although it was not direct evidence for the validity of GI and GL, and the GI values were comparable to published data for GI of Korean foods.[43]

Regardless of these limitations, rice is a major staple among two-thirds of the world's population,[44] thus it is worthwhile to note different association between brown rice (whole grain) and white rice (refined grain) with breast cancer risk, as well as results of carbohydrate measures.

In conclusion, results do not support an association between breast cancer and diets high in carbohydrate, glycemic index, or glycemic load and indicate that brown rice with cereals and beans instead of white rice may be related to a decreased risk of breast cancer among overweight, postmenopausal women.

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AUTHOR DISCLOSURES

We declare that we have no conflict of interest.

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Original Article

The association of carbohydrate intake, glycemic load, glycemic index, and selected rice foods with breast cancer risk: a case-control study in South Korea

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醣類攝取、升糖負荷、升糖指數及米食與乳癌危險性之相關：一個南韓的病例對照研究

雖然醣類被假設與乳癌的發生有關，但醣類攝取的評量與乳癌危險性的相關仍不清楚。我們在一家醫院進行病例對照研究，評估乳癌危險性與總醣類攝取、升糖負荷、升糖指數、及米的種類的相關性。病例組為 362 名婦女，年齡 30-65 歲，都經組織檢驗證實罹患乳癌。對照組婦女在同一家醫院就診，與病例組依年齡(±2 歲)和停經狀況配對。飲食攝取以列有 121 項目的定量式飲食頻率問卷(FFQ)評估。使用條件式及非條件式邏輯迴歸分析，求得勝算比(OR)及 95%信賴區間。結果發現，罹患乳癌的危險性與醣類攝取及升糖負荷沒有相關性。但與白米攝取有正相關 (OR=1.19 每增加 100 g/天，95% CI=1.01-1.40)；與混合白米沒有相關性(OR=0.95 每增加 100 g/天，95% CI=0.80-1.13)，與混合糙米為負相關(OR=0.76 每增加 100 g/天，95% CI=0.61-0.95)。進一步分析顯示，在體重過重的停經後婦女，乳癌危險性與白米攝取有正相關，與混合糙米攝取為負相關。這些結果並不支持乳癌與高醣飲食、升糖指數或升糖負荷的相關性。然而，攝取較多的混合糙米可能與降低乳癌危險性有相關，尤其是在體重過重的停經後婦女。

關鍵字：醣類、升糖負荷、升糖指數、米、乳癌